37. **(Canceled)**

38. **(Canceled)**

39. ~~(New)~~ The method of claim 38, wherein said ubiquitin-dependent proteolysis is by the proteasome.

40. **(Cancelled)**

41. **(Currently amended)** The method of claim 36, wherein the F-box is from an F-box polypeptide [is] selected from the group consisting of Cdc4p, Pop1p, Pop 2p, Grr1p, Met30p, HOSp, beta TrCPp, and FWD1p.

42. **(Currently amended)** The method of claim 36, wherein the F-box is from an F-box polypeptide [is a polypeptide] comprising an amino acid sequence selected from the group consisting of SEQ ID Nos. 2, 4, 6, 8, 10, and 12.

43. **(Currently amended)** The method of claim 36, wherein the F-box is from an F-box polypeptide [is] encoded by a nucleic acid selected from the group consisting of SEQ ID Nos. 1, 3, 5, 7, 9, and 11.

44. **(Currently Amended)** The method of claim 36, wherein the F-box [polypeptide] is at least [70] 95% identical to a contiguous polypeptide sequence of a polypeptide selected from the group consisting of SEQ ID Nos. 2, 4, 6, 8, 10 and 12.

45. **(Currently Amended)** The method of claim 36, wherein the F-box [polypeptide] is encoded by a nucleic acid that hybridizes under stringent conditions comprising a wash step in 0.2 x SSC at 50°C to a nucleic acid selected from the group consisting of SEQ ID Nos. 1, 3, 5, 7, 9, and 11.

46. The method of claim 36, wherein the target polypeptide is targeted for proteolysis in vitro.

47. **(Currently Amended)** The method of claim 36, wherein the target polypeptide is targeted for proteolysis in a yeast cell *in vivo*.

48. The method of claim 36, wherein the target polypeptide interaction domain is selected from the group consisting of a papillomavirus E7 polypeptide, and an SV40 LTP polypeptide.

49. The method of claim 36, wherein the target polypeptide is selected from the group consisting of a retinoblastoma polypeptide, a p107 polypeptide, IkB, Sic1p, Cln2p, E2 or beta- catenin.

Remarks

Claims 36-49 are currently being examined. Claims 37, 38 and 40 have been canceled. Claims 36, 42-45 and 47 have been amended. Support for the claim amendments may be found throughout the specification, including the claims as originally filed. In particular, support for the amendment to claim 45 can be found at page 29, lines 9-16. No new matter has been added.

Amendment of claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The amendments to the claims are being made solely to expedite prosecution of the present application. Applicants reserve the option to further prosecute the same or similar claims in the instant or in a subsequent patent application.

Applicants respectfully acknowledge Examiner's renumbering of claims 44 and 45 to claims 55 and 56, respectively.

Rejection of claims 36-40 and 45-49 under 35 U.S.C 112, first paragraph

The Examiner states that claims 36-40 and 45-49 stand rejected under 35 U.S.C. 112, first paragraph because, according to the Examiner, they describe subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the invention at the time the application was filed. The rejection is respectfully traversed.

Examiner states that claims 36-40 and 45-49 "are directed to a genus of hybrid polypeptides comprising F-box polypeptide and a target interaction domain" and "'F-box polypeptides' encompass proteins of diverse structures and, in many cases, unknown function." The Examiner further states that "the specification does not contain any disclosure of the structure and function of all hybrid polypeptides comprising F-box polypeptide and a target interaction domain" and, as a result, "many structurally and functionally unrelated F-box and hybrid polypeptides are encompassed within the scope of these claims."

Applicants respectfully submit that an Applicant "may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997)."

F-box polypeptides contemplated in this invention (as indicated in the rejected claims) are F-box containing proteins that are members of the SCF (**S**kp1, **C**ullin, **F**-box-containing

protein) ubiquitin protein ligase complex (see, for example, page 4). The SCF complex is important in targeting ubiquitin dependent proteolysis. The role of F-box containing proteins, in particular, is to recruit target polypeptides to the core SCF complex for ubiquitination and subsequent degradation (see page 5). As is explained on page 5 of the disclosure, an F-box containing protein comprises an F-box domain, which binds to the Skp1 protein, and may contain additional protein-protein interaction domains, such as WD40.

The specification is replete with descriptions and examples of F-box containing proteins. For example, on page 13, lines 2-10, a listing of F-box containing proteins is provided. As is disclosed in the specification, the F-box containing protein may be Cdc4p, Pop1 , Pop 2, Grr1p, Met30p, HOS, beta TrCP, FWD1 or a structurally related variant. In addition, the amino acid sequences of six F-box containing proteins are disclosed in the specification (see SEQ ID NOs: 2, 4, 6, 8, 10 and 12). Furthermore, page 31, lines 12-17, disclose an even more extensive list of F-box containing proteins. The specification further teaches that any of the F-box containing proteins disclosed in Bai et al. ((1996) Cell 86:263) may be utilized in the present invention.

A discussion of the structural determinants of an F-box are also provided in the specification. Page 31, lines 3-24 of the specification provides a functional and structural description of an F-box. In particular, the specification points out that the F-box of the h-βTrCP, corresponding to SEQ ID NO:4, corresponds to amino acids 148-192. The specification further teaches that Bai et al., *supra*, discloses an alignment of the F-box domains of F-box containing proteins and derives a consensus sequence. Based on the consensus sequence for F-box proteins, a person of ordinary skill in the art could readily identify F-box containing proteins.

In addition, Applicants have provided working examples of F-box containing fusion proteins, wherein the F-box protein is Cdc4p and βTrCP.

The Examiner further states that "there is no showing that F-box is sufficient to impart the requisite function." Applicants submit that an F box is sufficient in at least some F box proteins, however, merely for expediting prosecution of the this application, the claims have been amended to recite fusion proteins comprising a WD40 domain.

Therefore, Applicants respectfully submit that the written description discloses a representative number of species of the claimed genus. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of claims 36-49 under 35 U.S.C 112, first paragraph

The Examiner objects to claims 36-49 under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to "enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims." Specifically, the Examiner states that "while being enabling for a method of degradation of target polypeptides using hybrid polypeptides comprising Cdc4/βTrCP and known target polypetide interaction domain, such as LTP and E7N, in yeast and human cells, respectively, does not reasonably provide enablement for a method of use of a hybrid comprising any F-box polypeptide for which target polypeptide and ubiquitin proteolysis pathway is unknown." Applicants respectfully traverse this rejection.

It is a well-settled tenet of patent law that "mere breadth" is not a proper test under this section. See, In re Marzocchi et al., 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). Furthermore, the Federal Circuit has also held that a "patent specification [is] enabling even though it listed elements that could form thousands of end products, some of which may not be operative." Atlas Powder Co. V. E.I. du Pont de Nemours & Co., 224 U.S.P.Q. 409 (Fed. Cir. 1984). Accordingly, even if the claims were to read on some inoperative embodiments the law states that the specification would still meet the requirements of section 112.

Applicants note that a long pedigree of cases have held that there is no requirement of *a priori* knowledge of all specific embodiments of the claimed invention. Enablement is not precluded even if some experimentation is necessary. Applicants contend that the specification provides sufficient guidance with respect to constructing hybrid polypeptides, such that a person of ordinary skill in the art could make and use the claimed hybrid polypeptides without undue experimentation, relying on the specification and knowledge in the art. The teachings of the specification clearly enable the skilled artisan to make and use a vast range of hybrid polypeptides at least for the following reasons.

Applicants submit that the specification describes working examples of fusion proteins containing two different F-box proteins: fusion proteins containing pCdc4 and fusion proteins containing βTrCP (see Examples). Contrary to the Examiner's statement, βTrCP is not the human homolog of pCdc4. In fact, the human homolog of pCdc4 is termed Fbw7 or hCdc4 (Mitchell, (2001) Mol. Cell. Biol. Vol. 2, pg.785; Strohmaier, et al., (2001) Nature, Vol 413, pg. 316; Koepp et al., (2001) Science, Vol 294, pg. 173). As further described herein, the specification describes numerous other F-box proteins that can be used for constructing fusion proteins of the invention. Regarding target proteins, Applicants submit that the specification provides working examples of three different target proteins: pRb, p107 and the viral protein E2 (see Examples). In addition, Applicants have successfully targeted other cellular proteins, e.g.,

p130, a retinoblastoma protein family member (unpublished results). Applicants have found that any cellular protein chosen could successfully be targeted by the claimed method. Accordingly, the specification enables a person of skill in the art to make and use the invention commensurate with the scope of the claims. Each of the Examiner's issues are addressed separately below.

It is the Examiner's position that "'F-box polypeptides' encompass proteins of diverse structures and, in many cases, unknown function." Applicants respectfully submit that, as described above under the written description arguments, F-boxes that target polypeptides to the ubiquitin degradation pathway (as required by the rejected claims) share sufficient structural features to be distinguished from other proteins. Regarding function of F-box polypeptides, the rejected claims cover only those F boxes that target polypeptides to the ubiquitin degradation pathway. A person of skilled in the art can readily determine whether an F-box polypeptide or portion thereof has this biological function (see, e.g., the Examples).

The Examiner further stated, that "ubiquitin proteolysis pathways are not yet elucidated in most settings" and that "[w]ithout knowing the target interacting domain and its target as well as corresponding F-box protein, it is impossible to construct a requisite hybrid." Applicants respectfully submit that Applicants have shown that it is possible to target a protein to the ubiquitin degradation pathway by linking the protein to an F-box that targets a protein for degradation by the ubiquitin degradation pathway. Thus, it is not necessary to know the pathway by which a particular protein is normally degraded.

The Examiner also stated that "the specification teaches a method of use of a F-box polypeptide, Cdc4, and its human analog, βTrCP, fused to a known target polypeptide interaction domain, for degrading of a known target polypeptide *in vivo* in isolated yeast and human cells, respectively"(original emphasis). Applicants respectfully submit that, as set forth above, βTrCP is not the human homolog of Cdc4. Regarding target proteins, Applicants respectfully submit that other target proteins and target protein interacting domains can be used. Interacting domains are known for a significant number of target proteins. In addition, the specification describes how one may identify other interacting domains (pages 33 to 58). This section of the specification provides guidance regarding the identification of the second functional subunit of the hybrid polypeptide. In particular, this section of the specification teaches specific methods for identifying and isolating a target polypeptide interaction domain. Among the recited methods are the yeast two-hybrid or interaction trap, the yeast cytoplasmic two-hybrid, the mammalian two-hybrid or interaction trap, the far western, phage display, protein trap + nucleic acid snag, biomolecular interaction analysis and peptide matrix arrays. Table I on page 36 provides a summary of the general methods, along with references, that may be used to clone interacting proteins and pages 37-58 provide additional guidance on these methods. Based on the written

description provided in the specification and the advanced level of the knowledge in the art, Applicants respectfully submit that a person skilled in the art would readily be able to identify and isolate a protein interaction domain that could be used to construct a hybrid polypeptide of the present invention.

The Examiner further stated that "the specification fails to provide guidance as to the composition and structure and function of components of other ubiquitin ligases that can be used in the claimed method other than Cdc4 and its human homolog." Applicants respectfully submit that, as described above, the specification describes that several components of other ubiquitin ligases can be used. For example, the F-box domains of the following F-box polypeptides may be utilized in the current invention: Cyclin F, Skp2p, Pop1, C02F5.7, F48E8.7, MD6, YJL149w, N0376, 9934.4, 8039.5, N1161, SconB, Scon-2, fim, UFO, C02F5.7, C14B1.3, C17C3.6, C26E6.5, F43C9/1, F48E8.7, K10B2.1, T01E8.4, ZK328.7, Ro3D7, MD6, p110SIII, E3012.9K or βTrCP (page 31).

Additionally, Applicants respectfully remind the Examiner that "[a] specification is presumed to be enabling and the U.S. Patent and Trademark Office (PTO) has the burden of establishing a prima facie case of lack of enablement." In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). To make a prima facie case of lack of enablement, the PTO must come forward with reasons, supported by the record as a whole, showing why the specification fails to enable one of ordinary skill in the art to make and use the claimed invention. Id. The burden is on the PTO to establish that experimentation would be undue, taking into consideration the eight factors that are to be considered in determining whether a disclosure requires undue experiment. In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). In applying these eight factors to the instant case it is evident from the above discussion that the level of skill in this art was very high at the time the application was filed, and the experimental techniques needed to practice the invention were well known and exemplified in the specification as filed. Accordingly, Applicants respectfully submit that armed with the teachings of the specification and the contemporary knowledge in the art, the skilled artisan would be able to practice the claimed invention without further undue experimentation. Routine screening techniques taught in the specification combined with those techniques available in the art at the time the present invention was made provide sufficient guidance for generating hybrid fusion proteins comprising an F-box domain and a target protein interaction domain. Accordingly, Applicants assert that the specification, in light of the art at the time the present invention was made, is enabling for a sufficient number of other permutations of the hybrid polypeptides proteins to entitle Applicants to the invention as presently claimed.

The Examiner additionally objects to claim 44 under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, because "the specification, while being enabling for a hybrid protein comprising F-box polypeptide of SEQ ID NO:4, does not reasonably provide enablement for a hybrid protein comprising F-box polypeptide having 70% homology to SEQ ID NO:4." Applicants respectfully submit that the specification provides sufficient guidance to enable one skilled in the art to make an use the claimed invention. The specification contains both the meaning of sequence identity, page 18, lines 6-17, and methods for determining the percent identity between sequences, page 20, lines 13-30. Additionally the specification teaches how one skilled in the art could generate functional homologs of the claimed polypeptides by mutagenesis, truncation or chemical modification page 27, lines 9-30. Importantly, the specification does provide guidance for modifying an F-box polypeptide without sacrificing biological function. For example, the disclosure provided on page 27, lines 23-30 and page 28, lines 1-11, provides guidance as to which amino acids are considered conservative and would therefore be unlikely to affect protein function. Additionally, pages 28-30 provide methods for generating libraries of potential homologs and screening such homologs for a gene products for functional equivalents. Finally, page 31, lines 3-24, provides guidance regarding the location and amino acid composition of an F-box domain of an F-box polypeptide. Bai et al., discussed in the specification on page 31, lines 20-24, provides the position of conserved residues within the F-box domain. Based on these teaching provided in the specification, one skilled in the art would be able to predict which amino acids may be modified "without affecting F-box activity." Considering the level of skill in the art and the teachings provided in the specification, Applicants respectfully submit that one skilled in the art could make the claimed invention without undue experimentation. However, solely to expedite prosecution, Applicants have amended the claim to recite 95% homology.

In view thereof, reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph, rejection are respectfully requested.

Rejection of claims 36-49 under 35 U.S.C. 112, second paragraph

Claims 29-48, 50, 55 and 56 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Claim 36 was rejected for reciting "F-box" polypeptide because, according to the Examiner, "there is no clear definition of this term either in the art or in the specification" and this "renders the metes and bounds of the claim unascertainable." Furthermore, claims 37-49 are

rejected as dependent from claim 36. As pointed out above, the specification clearly defines "F-box" and the claim requires the F-box to target the hybrid polypeptide for ubiquitin-dependent proteolysis. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 36 was rejected for being "confusing as drawn to 'a method for degrading a target polypeptide' while, in fact, reciting a method for targeting. Further, claim 36 is incomplete as omitting essential steps, such omission amounting to a gap between the steps. The omitted steps appear to be steps recited in claims 37 and 38." Claim 36 has been amended and the amendment is believed to obviate the rejection. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 37 and 38 were rejected as "confusing because they recite steps that should precede the step of 'degrading a target polypeptide' recited in claim 36 from which claims 37 and 38 depend." Claims 37 and 38 have been cancelled, thereby rendering the rejection moot.

Claim 37 was rejected for reciting "SCF" since the Examiner considers it "unclear which molecules other than SCF complexes of S. cerevisiae are encompassed by the claim." Claim 37 has been cancelled, thereby rendering the rejection moot.

Claim 41 was rejected for reciting "beta TrCPp" since the Examiner considers it unclear "which molecules other then SEQ ID NO:4 are encompassed by the claim." Applicants respectfully submit that, e.g., molecules from species other than human are encompassed by the claim.

Claim 45 was rejected for reciting "stringent conditions," since, according to the Examiner, "it is impossible to determine which molecules are included in the scope of the claim." Claim 45 has been amended and the amendment is believed to obviate the rejection. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 46 and 47 were rejected for reciting "in vitro" and "in vivo," since in vivo may be construed as a live organism. Claim 47 has been amended and the amendment is believed to obviate the rejection. Reconsideration and withdrawal of the rejection is respectfully requested. Applicants respectfully request the Examiner to point out why claim 46 is rejected.

Rejection of claims 36-39, 45, 46, 48 and 49 under 35 U.S.C. 102(b)

Claims 36-39, 45, 46, 48 and 49 have been rejected under 35 U.S.C. § 102 (b) as being anticipated by Scheffner et al. (Virology 199: 448-452 (1994), form PTO-1449 mailed January 28, 2002 reference BF). The Examiner states that of Scheffner et al. "teach degradation of the retinoblastoma protein by human papilloma virus type 16 (HPV-16) E7-E6 proteins in vitro" and

that "absent clear definition of 'F-box polypeptide,' E-6 is construed as an F-box polypeptide." Applicants respectfully traverse the rejection.

Applicants respectfully point out that, while the E6 protein is a viral oncogene capable of targeting the oncogene p53 for degradation via the E2/E3 complex (UbcH8 and E6-AP respectively), the cellular mechanism of action of E6 is distinct from that of an F-box containing protein. The action of E6 is mediated by E6-AP (E6 associated protein) a E3 ubiquitin protein ligase. As is stated in the specification, page 7, lines 3-19), the E6-AP genes belong to the HECT family of E3 proteins. The HECT protein ligase family is distinct from the SCF family of E3 proteins, which include F-box polypeptides. As set forth above, F-box is clearly defined in the specification and does not include E6.

Examiner further states that "[c]laim 45 is included in the rejection because a DNA encoding E6 can hybridize to SEQ ID NO:4 under some undefined conditions." Applicants respectfully point out that a BLAST comparison of SEQ ID NO:4 and the gene encoding E6 reveals no significant sequence similarity between the two proteins, and therefore, as a result, a DNA encoding E6 would not be expected to hybridize to SEQ ID NO:4 under the stringency conditions recited.

Conclusion

In view of the above remarks and the amendments to the claims, it is believed that this application is in condition for allowance. If a telephone conversation with Applicant's Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 832-1000.

Respectfully submitted,

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